

Successful Treatment with Regimen of Intravenous Gammaglobulin and Cyclophosphamide for Dermatomyositis Accompanied by Interstitial Pneumonia, Opportunistic Infection and Steroid Psychosis

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ABSTRACT

Background: A 47-year-old Japanese woman was suffering from dermatomyositis with progressive interstitial pneumonia, which was resistant to treatment with prednisolone (Pred) and cyclosporine A (CsA). Unfortunately, the opportunistic infection and steroid psychosis made therapeutic intervention using additional immunosuppressive drugs problematic. To overcome these difficulties, we created a regimen of intravenous gammaglobulin (IVIG) and cyclophosphamide (CPM) for the treatment of this patient.

Methods: For the simultaneous treatment, IVIG-CPM was added to Pred/CsA by means of infusion of IVIG on five consecutive days per month, followed by CPM infusion on the ninth day after the last IVIG administration. The treatment was repeated for four months.

Results: This regimen induced almost full remission without exacerbation of the opportunistic infection or mental disturbance.

Conclusions: The outcome reported here suggests that the combination therapy of Pred/CsA and IVIG-CPM appears to be useful for the treatment of dermatomyositis with pulmonary, infectious and mental complications.

KEY WORDS

combination, dermatomyositis, gammaglobulin, immunosuppressive drugs, interstitial pneumonia

INTRODUCTION

Dermatomyositis (DM) is associated with high morbidity and mortality rates, primarily related to muscle weakness, cardiac and lung impairment, as well as infections. Many modes of intervention are available for the treatment on this condition including corticosteroids,¹ immunosuppressive drugs such as CPM,²⁻⁴ IVIG therapy,⁵⁻⁷ and plasmapheresis.⁸ Although combinations of these therapeutic interventions are often adopted for intractable cases of this disease,^{9,10} the relatively frequent occurrence of complications con-

sisting of opportunistic infection and steroid psychosis have made treatment with additional immunosuppressive medications problematic. Here we describe our experience with a combination treatment regimen of IVIG and CPM in a patient with DM, whose course of therapy was hampered by complications.

CLINICAL SUMMARY

A 47-year-old woman presented with complaints of easy fatigability and muscle weakness causing difficulties especially when climbing stairs. These complaints had developed in conjunction with a DM-

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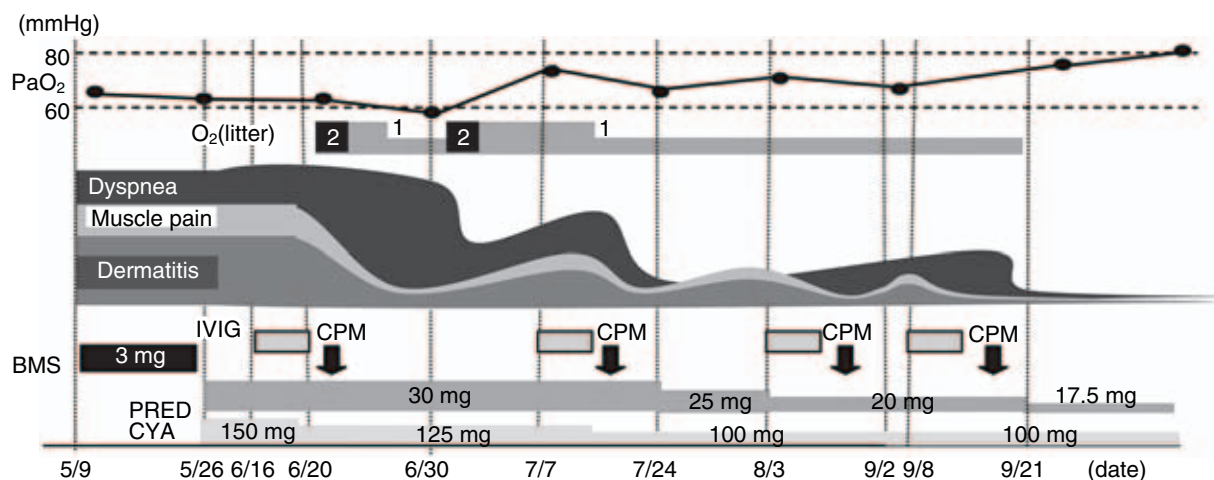


Fig. 1 Scheme of clinical course in this case. BMS, betamethasone; Pred, prednisolone; CsA, cyclosporine A; CPM, cyclophosphamide; IVIG, intravenous gammaglobulin.

associated rash. The patient also reported episodes of clinical depression following administration of betamethasone (BMS) for DM.

DM had been diagnosed in 2002, when the patient was 46, based on the presence of a characteristic dermatitis, including a heliotrope rash, Gottron papules, and poikiloderma, which was accompanied by proximal muscle weakness and elevated muscle-derived enzyme levels. Treatment following diagnosis consisted of 3 mg/day of BMS and topical treatment. However, the skin continued to show signs of DM and muscle weakness abated only occasionally. Moreover, steroid psychosis developed after about four months of BMS treatment.

When the patient visited our outpatient clinic for consultation, she was suffering from DM-associated rash, proximal muscle weakness, acute respiratory distress, and a mental disorder. These symptoms significantly interfered with the activities of her daily life.

Laboratory examination findings showed an elevated aldolase level of 36.2 U/L (normal, < 7.2 U/L), anti-nuclear antibodies (homogenous, $\times 40$), and an elevated KL-6 level of 944 U/ml (normal, < 500 U/ml). Magnetic resonance imaging (MRI) analysis showed inflammation of the quadriceps femoris muscle, and computed tomographic (CT) scan of the lung signs of non-specific interstitial pneumonia. On the other hand, diagnostic imaging analysis indicated no internal malignancy. The use of Pred instead of BMS was recommended, and if the response was inadequate, of oral CsA.

On admission, BMS was switched to 30 mg/day of Pred and 100 mg/day of CsA for the first 21 days. Although steroid psychosis was suppressed by administration of paroxetine, exacerbation of muscle weakness, DM-associated rash, and interstitial shadows on the lungs were observed, as well as dyspnea accom-

panying a daily reduction in oxygen partial pressure (PaO₂). Furthermore, cytomegalovirus (CMV) infection was confirmed by immunological staining of leukocytes by using the monoclonal antibody HRP-C7. Ophthalmoscopic examination disclosed some small white punctate lesions resembling cotton-wool spots in the macular area of both eyes, which is thought to be the earliest sign of CMV retinitis. These lesions showed regression in response to 7.5 mg/kg of ganciclovir per day. There was recurrence of CMV retinitis signs after withdrawal of ganciclovir infusion, but these signs began to regress after ganciclovir infusion was started. However, respiratory symptoms and signs were not improved by ganciclovir infusion. The absence of other opportunistic infections clearly indicated that this progressive interstitial pneumonia was caused by the exacerbation of DM. It seemed advisable to treat the primary disease with additional immunosuppressive drugs such as methylprednisolone pulse therapy or CPM, but complications from opportunistic infection and steroid-induced depression made the application of such treatments problematic. The efficacy of IVIG for DM and opportunistic infections has been demonstrated, but not for interstitial pneumonia. In view of these problems, simultaneous treatment with IVIG-CPM was added to Pred/CsA treatment. IVIG infusion (4 g/kg body weight/day)⁶ was performed on five consecutive days per month, followed by CPM infusion at 500 mg/day, equivalent to about 10 mg/kg body weight,⁴ on the ninth day following the last IVIG administration. From the first month of treatment, the clinical status and the respiratory symptoms gradually recovered together with improvement in ALD and PaO₂ values (Fig. 1). No new major side effects were observed during the regimen.

The patient was given three courses of the regimen

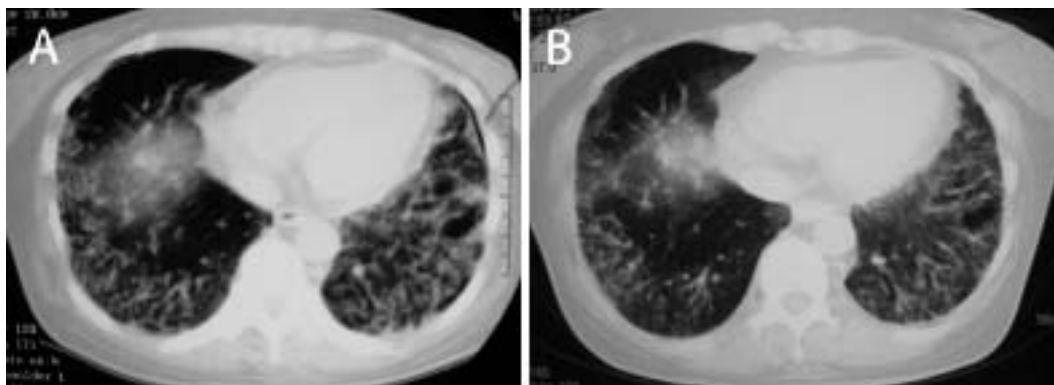


Fig. 2 CT scan of the lung. (A) before combination therapy, and (B) after the completion of all combination therapeutic courses.

of IVIG/CPM infusion over four months and after all courses were completed, marked improvements detected in clinical symptoms and laboratory findings, and observed on CT scans or MRI images were confirmed (Figs. 1,2). For 8 months after the final discontinuation of this regime, the patient's condition has remained good with the administration of 17.5 mg/day of Pred and 100 mg/day of CsA.

PATHOLOGICAL FINDINGS

A skin biopsy confirmed the diagnosis of DM by demonstrating characteristic interface dermatitis with mucin deposition (data not shown).

DISCUSSION

The most effective treatment of DM is still a matter of debate. It has been frequently reported that corticosteroids constitute the mainstay of the treatment with IVIG and other immunosuppressants added for difficult cases. However, it has recently been pointed out that these immunosuppressive medications may be implicated in the apparent increase in the frequency of opportunistic infections. Isabelle *et al.*,¹¹ in a study of 156 consecutive polymyositis (PM)/DM patients, reported a prevalence of opportunistic infections of 11.5%, and that the mean daily dose of steroids was higher in patients with opportunistic infections than for those without (57.3 and 26.6 mg, respectively). Opportunistic infection occurred in 62.5% of cases during the first year following PM/DM diagnosis. Although the majority of patients may receive high doses of steroids during this period, 12.5% of PM/DM patients had not been exposed to steroids at the onset of opportunistic infections. These findings indicate that immune system dysfunction due to PM/DM itself may lead to elevated susceptibility to opportunistic infections. IVIG concentrates were originally developed as a replacement therapy for individuals with primary deficiencies of the immune system. However, recent studies have demonstrated the abil-

ity of IVIG to prevent and possibly treat infections in patients with secondary immune deficiencies. IVIG have additional beneficial effects, especially on the skin and muscle manifestations of DM. In view of these findings, IVIG treatment is assumed to be beneficial for the symptoms and complications associated with DM. On the other hand, the efficacy of IVIG treatment for interstitial pneumonia with DM is still controversial. Interstitial lung disease (ILD) is a well-recognized manifestation of PM/DM, and previous studies have reported a prevalence of interstitial lung disease ranging from 10% to more than 50%.¹² Progressive ILD is distinguished from the nonprogressive version by extensive areas of ground-glass opacity on high-resolution computed tomography (HRCT) and by bronchoalveolar lavage (BAL) neutrophilia.¹² While BAL of our patient was not examined, the HRCT scan showed extensive diffuse areas of bilateral ground-glass and reticular opacities, and the abnormalities involved both the central and peripheral lung zones. Furthermore, arterial blood gas analysis in room air indicated daily hypoxemic deterioration. Intravenous CPM pulse therapy is known to be useful for the treatment of progressive ILD.^{4,13,14} For our patient, too, intravenous CPM pulse therapy gradually led to improvement in respiratory symptoms, while application of Pred, CsA, and IVIG did not stop the progression of ILD. It was even more remarkable that no relapse of CMV retinitis was observed after simultaneous treatment with IVIG-CPM. In the past, efficacy of treatment with IVIG and CPM in DM/PM has been disputed. There are two articles which describe a treatment by IVIG together with low-dose oral administration of CPM in DM/PM.^{15,16} Chang *et al.*,¹⁶ reported that oral administration of CPM (2.2 mg/kg) improved the clinical manifestations of IVIG-resistant Evan's syndrome associated with DM. But there have been no reports which mention simultaneous treatment with IVIG and intravenous pulse-CPM. Our case suggests that the newly constructed regi-

men of IVIG and CPM may produce low-risk improvements in the symptoms of Pred- and CsA-resistant DM associated with progressive ILD. At the same time, Pred and CsA are effective for the maintenance of a good overall condition of the patient. It can therefore be assumed that the synergistic application of these treatments may result in a better therapeutic effect.

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